Acute leukemia: Endpoints that reflect “living better”

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Outline

- Measures of “living better”
  - Patient reported outcomes
  - Clinical events
- FDA experience
- Challenges
- Considerations in acute leukemia
- Conclusions/speculations

Background

- Criteria for FDA approval: “Live longer, live better”
- “live longer”
  - Survival
  - Disease-free survival
  - Time to progression

Living better

- Derives from 2 possible effects of a new therapy
  - Improvement of disease symptoms compared to standard
  - Reduction of therapy side-effects compared to standard

Potential measures of “living better”

- Patient reported outcomes (PROs)
  - Symptom relief (fatigue, pain - scales)
  - Better HRQOL (multi-dimensional: physical, functional, social, emotional, spiritual – QOL instruments)
- Fewer clinical events/outcomes
  - transfusions, TPN days, hospital days, days of antibiotics or antifungals – recorded in CRFs
  - Less toxicity (blood counts, mucositis - CTC criteria)

FDA and PRO's

- PhRMA Health Outcomes workshop 1999
  - HRQOL is a measure of effectiveness and should be treated as any other clinical endpoint
- PRO Harmonization Group: February 2002
  - Commitment for further discussion of methodologic standards for measuring and interpreting PRO's
- PRO's in approved product labels (Controlled Clinical Trials 2004)
  - 1997-2002: 21 cancer approvals of NMEs – 1 using a PRO (Samarium for pain relief in bone cancer)
  - Of the other drugs using PROs, most use specific symptoms

FDA and PRO's

- PRO's used have almost always been specific symptoms assessed by specific symptom scales
- Evidence of use of global HRQOL for approval is lacking.

Symptom relief

- Challenge is development/refinement of instruments that have demonstrated validity, reliability, and are sensitive to clinically important changes (same as for HRQOL)
- PROMIS network
- Instruments
  - FACT- fatigue (FACT-G plus fatigue – 13 items within anemia)
  - FACT – anemia (20 items +FACT-G)
- These hold promise especially for drugs that target specific symptoms
- May miss other toxicities or changes in global QOL

Quality of life assessment

- Multidimensional (symptoms, physical, spiritual, cognitive, emotional functions)
- Health-related QOL: aspects attributable to
  - Health
  - Disease
  - Treatment
- Many inputs affect HRQOL outcomes beside the drug of interest
- In theory, HRQOL is best assessment of “living better”

Quality of life assessment

- Ask the patient (or proxy)
- Instrument must be
  - Validated, reliable, sensitive to change
  - Multi-dimensional

Advantages of QOL endpoints

- Integrates benefits and harms of therapy
  - Enhanced survival may come at an extreme cost
  - WIWI – “was it worth it?” Sloan JCO
- Reflects patient experience
- Clearly important if efficacy similar

Challenges assessing QOL

- Lack of robust tools to measure QOL in leukemia
  - FACT-LEUK (nascent), EORTC-LEUK
  - Pedi Cancer QOL Inventory (cancer generic and nascent)
- Difficulties collecting QOL data (logistics, non-compliance)
- Missing data (drop out, missing repeated measures, not filled out completely)
- Complicated analytic approaches (missing data, repeated measures over time)

Challenges assessing QOL

- Often need a greater N than clinical endpoints to achieve statistical significance
- Subjective endpoints affected by many factors (including non-medical), thus suspect
- Difficulty understanding minimal clinical differences
  - Distribution of scores
  - Use clinical anchor
- Communicating results to patients and physicians is challenging (what does a change in 10 HRQOL points mean?)

Research activity: QOL in leukemia

- AML
  - MRC 10 trial used EORTC QLQ-30 1 yr following treatment. Worse QOL in Allo-BMT compared to CCT or Auto-BMT (Eur J Cancer, 2004)
  - MDS: Azacytidine associated with better QOL (EORTC QLQ-30) compared to supportive care (JCO 2002) – complicated analysis and results display.
- ALL -
- CML – IRIS (imatinib v interferon/ara-C), used FACT-BRM. Better QOL with imatinib (JCO 2003).

FDA and clinical events

- Gemcitabine and pancreatic cancer
- clinical benefit response (CBR)
  - the pain "index" which includes pain intensity scoring and analgesic consumption
  - performance status (KPS)
  - one secondary measure: weight change.

Clinical events/outcomes

- days anti-infective drug use (antibacterials, antifungals)
- blood product transfusions
- days hospitalized
- reductions could derive from improvement in disease or reduced side-effects of treatment
- Composite score (combine clinical events)

Clinical events

- Easy to measure
- Objective
- Face validity
  - Self-evident?
- No known relationship to HRQOL

When to assess “living better”?

- if survival is about the same
  - are tradeoffs appropriate when survival rates differ?
- when subsequent non-protocol treatment (e.g. HSCT) confound disease benefit assessments

Special Considerations in Acute Leukemia

- Systemic disease – not site-specific
- New drugs for leukemia – targeted therapies often tested in relapsed setting and patients go on to stem cell transplantation
- Standard treatments are quite toxic
- Treatment-related morbidity and mortality high compared to other cancers
- Enhance the potential value of assessing “living better”

Addressing limitations - tools

- Develop robust instruments sensitive to QOL issues in leukemia/targeted therapy trials – reliable, valid, sensitive to change
- Demonstrate relationship between toxicity, clinical events, symptoms and QOL
- Determine minimal clinical differences of measurements

Addressing limitations - trials

- Pre-specify primary and secondary QOL endpoints and analytic plans
- Ensure adequate power for hypothesis testing
- Attention to data collection techniques to minimize missing data
- Randomization and blinding if possible

Conclusions

- Drugs that allow patients to live better are valuable additions to the treatment armamentarium and should be made available
- Methodologic barriers to proving that a drug allows a better life using HRQOL as an endpoint are daunting
  - Many inputs (beside the drug of interest) affect HRQOL introducing complex variability to the measure
  - Obligates larger “N”
  - Instruments that work and are accepted

Conclusions

- Symptom control as assessed by a symptom-specific instrument has been used for drug approval
- Clinical composite score – if measure had validity, could be used in drug approval
  - Composite score of transfusion and infection events in acute leukemia?
- HRQOL as an endpoint for drug approval is a laudable “work in progress”

Implication/speculation

- HRQOL will be a useful endpoint for assessment of drug approval in acute leukemia
- Composite clinical endpoints have more immediate potential for use in the proper setting